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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,927	11/01/2006	David Frederick Horrobin	56170/316314	6561

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,927	HORROBIN ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/05; 12/05; 9/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 1, 2006. Currently, claims 1-6 are pending.

Priority

2. This application is a 371 of PCT/GB03/05131, filed November 26, 2003 and claims priority to foreign application UK 0228079.0, filed December 2, 2002.

1.105 Request

3. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

A) Puri et al. (Neurology, Vol. 65, pages 286-292, 2005), of which Dr. Horrobin is named as a co-author, along with Dr. Manku and Dr. Murchk, states unpublished data with respect to ethyl-EPA and CAG repeats was available. Moreover, Dr. Murck and Dr. Manku (Brain Research Bulletin, Vol. 72, pages 159-164, 2007) states that two randomized placebo controlled trials are ongoing to determine, if the beneficial effects of Ethyl-EPA can be replicated.

Applicant and the assignee of this application are requested to provide data and results for any additional studies, trials, or experiments which analyze administration of eicosapentaenoic acid in any bioavailable form and CAG repeats in the Huntingtin gene.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting the number of CAG repeats in the Huntingtin gene and administering EPA to individuals, does not reasonably provide enablement for preventing development of symptoms by administering EPA or

selectively administering EPA to individuals with 45 or fewer repeats. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-2 are drawn to a method of identifying patients with Huntington's disease, or individuals at risk of developing Huntington's disease, who will respond to treatment with EPA by determining the number of CAG repeat in the Huntingtin gene and identifying those subject with 45 or fewer repeats.

Claims 3, 5 are drawn to a method of treating Huntington's disease by identifying patients having 45 or fewer CAG repeats in the gene for Huntingtin and administering to those patients EPA.

Claims 4, 6 are drawn to preventing the development of symptoms in individuals who are at risk of developing Huntington's disease by identifying individuals having 45 or fewer CAG repeats in the gene for Huntingtin and administering to those individuals EPA.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches analysis of treatment of Huntington's disease with EPA.

Vaddadi et al. (Clinical Neuroscience and Neuropathyology, Vol. 13, pages 29-33, 2002) teaches a randomized, placebo-controlled, double blind study of treatment of Huntington's disease with unsaturated fatty acids. Vaddadi teaches all patients had HD with clinical signs confirmed by genetic testing. The number of CAG repeats ranged from 40-49. Vaddadi teaches that all patients were randomized, double-blind and placebo controlled. Vaddadi teaches the treatment included EPA (see page 30, col. 1). Vaddadi further teaches the results of the trial are consistent with those of three other studies, including one patient treated for >6 years and another for >3.5 years and taking pure ethyl eicosapentaenoate (page 32, col. 1).

Puri et al. (Clinical Neuroscience, Vol. 13, No. 1, January 2002) teaches a 6-mo randomized, placebo-controlled pilot study of EPA was carried out in 7 patients with advanced stage Huntington's disease. Puri concluded that the treatment with ethyl-EPA is associated with beneficial motor and MRI changes.

Rosser et al. (In Focus, Vol. 13, No. 2, February 2002, A21-A22) considers the two studies, namely the Puri and Vaddadi study which used EPA to treat Huntington's disease. Rosser expresses concerns about the very small sample sizes in the trials.

Rosser states that although statistical significance of efficacy is claimed in both cases, results based on such small numbers of patients must be treated with caution, because of the often reported bias to only publishing positive effects. Rosser states that we cannot know how many small negative trials have not been reported and thus risk of type 1 error is not known.

Puri et al. (Neurology, Vol. 65, pages 286-292, 2005) teaches analysis of treatment with ethyl-epa in Huntington disease. Although Puri states that significant interaction between treatment and a factor defining patients with high vs low CAG repeats, further studies of the potential efficacy of ethyl-EPA are warranted.

Murck et al. (Brain Research Bulletin, Vol. 72, pages 159-164, 2007) teaches those patients with a lower CAG repeat number, i.e. those with a late age of onset showed a statistically significant clinical improvement with Ethyl-EPA intake vs placebo intake. However, Murck teaches that controlled trials are ongoing to determine if the beneficial effects of Ethyl-EPA, which were observed previously can be replicated in current studies (page 162, col. 2).

While the state of the art and level of skill in the art with regard to the detection of any known polymorphic allele is high, the level of unpredictability in associating any particular allele with a specific phenotype is even higher. The high level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. After a screening assay identifies polymorphisms, it is

unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, physiological state, or drug metabolism or response. Lucentini (The Scientist; 2004, vol 24, page 20) teaches that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1 st complete paragraph).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing

conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification.

The specification provides no evidence that the study performed is replicable and is robust given the small samples. The specification, page 5, teaches that when change in TMS was compared in the placebo group and the ethyl-EPA group, there was a better outcome on ethyl-EPA than on placebo but this was not statistically significant. The specification however teaches that when patients were stratified on the basis of their CAG repeat numbers, a dramatic benefit of ethyl-EPA was uncovered. Patients who had CAG repeat number of below 45 showed a large benefit from ethyl-EPA. Placebo patients with CAG repeat number 45 and below deteriorated by an average of 5.3% whereas the same group of patients on ethyl-EPA improved over the year by 19.3%. This difference was highly significant (see page 5 of the specification). The patients who had 46 or more CAG repeats did not show any difference between the ethyl-EPA and placebo treatment. The specification however is directed to a small sample size which has not been replicated, as required of genetic analysis studies in the art. The specification provides no guidance to preventing any symptoms. The

guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims are drawn to determining the number of CAG repeats or identifying patients with 45 or fewer CAG repeats. The art teaches that individuals with less than 36 CAG repeats are normal. It is unpredictable that patients having 0-36 CAG repeats have Huntington's disease and would have or be at risk for Huntington's disease or require any treatment, as suggested by Claims 1, 3 or 4.

The art specifically teaches that the studies performed in the art and the specification require verification. Rosser expresses concerns about the very small sample sizes in the trials. Rosser states that although statistical significance of efficacy is claimed in both cases, results based on such small numbers of patients must be treated with caution, because of the often reported bias to only publishing positive effects. Murck teaches that controlled trials are ongoing to determine if the beneficial effects of Ethyl-EPA, which were observed previously can be replicated in current studies (page 162, col. 2). Moreover, Hirschorn, Lucentini, and Ioannidis each teach the difficulty in identifying true associations between genetic mutations and phenotypes. Here, the art, specifically states that the study is such a small number and would require replication and caution. Thus, it is unpredictable based upon the suggestions and teachings in the art regarding the CAG repeat length and EPA to make any treatment decisions or prevention analysis. Further experimentation and validation would be

required before the skilled artisan could practice the instant treatment, prevention or identification claims.

With respect to claims 4, 6, drawn to preventing the development of symptoms in individuals who are at risk of developing Huntington's disease, it is unpredictable that EPA would prevent any or all of the symptoms of Huntington's disease in either "normal" or individuals predisposed to Huntington's disease. The symptoms of Huntington's disease include three types of symptoms: movement, cognitive, and psychiatric. These symptoms are very generic and it is unpredictable that the administration of EPA would prevent hostility or irritability, dementia or clumsiness in any individual. Each of these symptoms may be caused by additional conditions, situations, for example. Normal individuals may become hostile or irritable in certain circumstances, for example road rage. There is no reasonable expectation that administration of EPA to an individual with 30 CAG repeats, for example, would prevent the development of hostile behavior such as road rage, for example. Additionally, neither the specification nor the art provide any evidence that the symptoms may be prevented even for individuals with 37-45 repeats. It is unpredictable that EPA could prevent the symptoms of Huntington's disease, absent evidence. The specification and the art do not appear to take family members from affected patients, study the CAG repeats and administer EPA to those family members with 37-45 repeats prior to the development of symptoms and make any analysis that symptoms are prevented. The individuals with 37-45 repeats may be predisposed to later onset, in which case the administration of EPA would be unnecessary. Further unpredictable and undue experimentation would be required to make any analysis as to whether symptoms may be prevented by prophylactic treatment with EPA.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where neither the specification nor the art teach the skilled artisan how to use the claimed invention as broadly as claimed. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association studies with phenotypes. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-2 are indefinite because it is not clear what is required by the instant claims. The preamble is drawn to a method of identifying patients with Hungtington's disease who will response to treatment with EPA, however the final step in the method is to identify subjects with 45 or fewer repeats. Thus, it is unclear whether the method is merely a method of identifying individuals with 45 or fewer repeats or whether the method requires something more.

B) Claims 1-2 are indefinite over the recitation "those subjects" because the claim lacks proper antecedent basis. The claims appear to be directed to identifying patients or individuals. The last line of the claim then refers to "those subjects" which is indefinite because it is unclear what "those subjects" is referring to.

C) Claims 1-2 are indefinite over the recitation "45 or fewer repeats". The art teaches that individuals with less than 36 CAG repeats are normal. The claim appears to be directed to identifying subjects with 45 or fewer, namely 0-36 repeats as patients or individuals at risk of developing Huntington's disease.

D) Claims 3, 5 are indefinite over the recitation "45 or fewer repeats". The art teaches that individuals with less than 36 CAG repeats are normal. The claim appears to be directed to treating Huntington's disease by administering to those patients EPA, which would include normal patients. It is unclear how you would treat Huntington's disease if the patient did not have Huntington's disease.

E) Claims 4, 6 are indefinite because it is not clear what is required by the instant claims. The preamble is drawn to a method of preventing the development of symptoms in individuals however the final step in the method is directed to administering to individuals EPA. Thus, it is unclear whether the claim requires merely administering EPA or a method of preventing development of symptoms.

F) Claims 4, 6 are indefinite over the recitation "45 or fewer repeats". The art teaches that individuals with less than 36 CAG repeats are normal. The claim appears to be directed to preventing symptoms of individuals who are at risk of developing Huntington's disease by administering EPA to individuals with 45 or fewer CAG repeats. It is unclear how patients with 0-36 are at risk of Huntington's disease.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Vaddadi et al. (Clinical Neuroscience and Neuropathyology, Vol. 13, pages 29-33, 2002).

It is noted that if the specification is enabling, then so is this reference, and the claims may be unpatentable over the teachings of this reference. If the reference is not enabling, neither is the specification, which would also make the claims unpatentable. The examiner is not able to choose based on the limited evidence provided which is the

more correct rejection, however either rejection would render the claims unpatentable. Therefore in the interest of compact prosecution, the examiner has made a superficially inconsistent art and enablement rejection and places the burden on the Applicants to distinguish his or her specification from the prior art and to point out how the specification goes beyond and elaborates upon what is taught by the previously published reference. In the instant case the specification and the scope of the claims clearly imply that it is possible to treat and prevent Huntington's disease by administration of EPA. If this is true than Vaddadi anticipates the claims 1-6 which require either "treating Huntington's disease' or "preventing the development of symptoms". If this is not true then Vaddadi still anticipates claim 1 which only requires a step of "determining the number of CAG repeats and identifying those subjects" which Vaddadi clearly does.

Vaddadi teaches a randomized, placebo-controlled, double blind study of treatment of Huntington's disease with unsaturated fatty acids. Vaddadi teaches all patients had HD with clinical signs confirmed by genetic testing. The number of CAG repeats ranged from 40-49. Vaddadi teaches that all patients were randomized, double-blind and placebo controlled. Vaddadi teaches the treatment included EPA (see page 30, col. 1). Vaddadi further teaches the results of the trial are consistent with those of three other studies, including one patient treated for >6 years and another for >3.5 years and taking pure ethyl eicosapentaenoate (page 32, col. 1).

With respect to Claim 1-2, Vaddadi teaches determining the number of CAG repeats and identifying those subjects with less than 45 repeats. Specifically, Vaddadi

teaches confirming HD diagnosis based upon CAG repeats. The patients in the study of Vaddadi ranged from 40-49 CAG repeats.

With respect to Claim 3, 5, Vaddadi teaches administering EPA to randomized patients. These randomized patients includes patients with 40-45 CAG repeats.

With respect to Claims 4, 6, to the extent the claims only require identifying individuals having 45 or fewer CAG repeats and administering EPA to those individuals, Vaddadi teaches determining the CAG repeats and administered EPA to a randomized sample of those individuals.

Conclusion

7. No claims allowable.

8. This Office action has an attached requirement for information under 37 CFR 1.105. A complete reply to this Office action must include a complete reply to the attached requirement for information. The time period for reply to the attached requirement coincides with the time period for reply to this Office action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine A Goldberg/
Primary Examiner, Art Unit 1634
October 24, 2008